Arterial graft deterioration one year after coronary artery bypass grafting

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Objective: Some arterial grafts have progressive narrowing or occlusion during the first postoperative year despite angiographic patency in the immediate postoperative period. This study analyzed the incidence and predictors of arterial graft deterioration.

Methods: We reviewed 778 distal anastomoses of arterial grafts in 243 patients who underwent off-pump coronary artery bypass grafting. All patients underwent both early and 1-year follow-up coronary angiography, with all arterial grafts patent on the early angiograms. Arterial graft deterioration was defined as diffuse graft stenosis or occlusion newly found at 1-year follow-up angiography.

Results: Graft deterioration was present in 13.8% (string sign, 6.9%; occlusion, 6.8%) of distal anastomoses. The incidence of graft deterioration was higher among cases of non–internal thoracic arterial graft (27.7% vs 6.0%, $P < .001$), non–left anterior descending coronary arterial anastomosis (19.1% vs 2.0%, $P < .001$), mild (≤75%) stenosis of the target coronary artery (26.0% vs 7.6%, $P < .001$), composite grafting (19.9% vs 7.8%, $P < .001$), and multiple anastomoses from a single inflow source (19.5% vs 5.1%, $P < .001$). The incidence was particularly high when composite or multiple grafting from a single inflow source was performed to a target coronary artery with mild stenosis. Non–internal thoracic arterial graft, mild target stenosis, and multiple grafting from a single inflow source were independent predictors of graft deterioration.

Conclusions: Arterial graft deterioration was closely related to particular graft materials and designs. (J Thorac Cardiovasc Surg 2010;140:1306-11)

The survival benefit of using a single internal thoracic artery (ITA) in coronary artery bypass grafting (CABG) was demonstrated in the mid 1980s,[1] and further beneficial effects of additional arterial graft use have been subsequently reported in several studies.[2-4] The clinical benefits provided by an arterial graft are usually considered to be related to superior patency.[5,6] The early failure of an arterial graft is rare and is related to several mechanisms, including anastomotic problems and poor quality of the graft material or the native coronary artery. Some arterial grafts, however, fail during the first year. Several studies have reported that some arterial grafts occlude in this time period, and this may result from competition with native coronary flow.[7,8] Other arterial grafts are reduced in caliber and show diffuse narrowing, the string sign. The incidence of string sign has not been negligible in some previous studies.[9,10] These findings suggest that some arterial grafts may lose the ability to function as a bypass conduit as a result of graft deterioration. In this study we therefore analyzed the incidence, predictors, and clinical consequences of arterial graft deterioration 1 year after CABG.

MATERIALS AND METHODS

Study Design

In this retrospective cohort study, we first examined a series of follow-up angiograms performed before discharge and 1 year after surgery and then investigated the predictors of arterial graft deterioration. In addition, we investigated the association between arterial graft deterioration and clinical outcomes. The Ethics Committee of Sakakibara Heart Institute approved this study, waived the need for patient consent, and provided approval before publication of the data.

Study Subjects and Data Collection

Between September 2004 and July 2007, a total of 536 patients underwent isolated CABG at our institution. All patients were scheduled for off-pump CABG. Twenty-five emergency cases were included. Six patients who had conversion to on-pump CABG were excluded from the study. We routinely performed coronary angiography before discharge and 1 year after surgery for patients who underwent off-pump CABG, regardless of the patient's symptoms. Patients who died, refused angiographic evaluation, were older than 75 years, or had renal dysfunction (serum creatinine >1.2 mg/dL) were excluded from the angiographic follow-up. Of the 536 patients, 432 underwent early angiography and 273 underwent 1-year follow-up angiography. For early angiography before discharge, 67 patients were excluded for old age, 15 were excluded for renal dysfunction, and 22 were excluded for patient refusal. For follow-up angiography at 1 year after surgery, 113 patients were excluded for old age, 24 were excluded

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
ITA = internal thoracic artery
LAD = left anterior descending artery

for renal dysfunction, and 126 were excluded for patient refusal. A total of 256 patients (47.8%) underwent both early and 1-year follow-up angiography. The angiographic results of these patients are shown in Table 1. Thirteen patients with multiple arterial grafting who had at least 1 occluded anastomosis were excluded from the study. Findings of the remaining 243 patients were retrospectively reviewed.

Perioperative clinical data were collected from patient medical records. All patients were followed up for at least 1 year, and mean follow-up was 21.8 months. A major adverse cardiac event was defined as the occurrence of a nonfatal myocardial infarction, the need for repeat revascularization, or cardiac death. Cardiac death was defined as death occurring in relation to myocardial infarction, cardiac arrhythmia, out-of-hospital sudden cardiac death, or deteriorating congestive heart failure. Undetermined causes of death were assumed to be cardiac.

One cardiologist initially reviewed all the coronary angiograms, and a consensus was reached among the surgical team after review. For native coronary arteries, mild stenosis was defined as a stenotic lesion of 75% or less. Distal anastomoses were assessed and classified as patent, focally stenosed, string sign, or occluded. A focally stenosed lesion was defined as one with a focal stenosis of 90% or greater anywhere within the conduit or at the anastomosis. String sign was defined as luminal narrowing throughout the entire conduit, including stenosis of 90% or greater. Each distal anastomosis represented a separate data point in the analysis. The patency rate was calculated as the number of distal anastomoses without occlusion per total distal anastomoses. Patent graft anastomosis included grafts with focal stenosis or string sign. Arterial graft deterioration was defined as a graft that had been patent on the early angiogram but appeared occluded or showed evidence of string sign on the 1-year angiogram. The incidence of arterial graft deterioration was calculated as the rate of distal anastomoses with arterial graft deterioration per total distal anastomoses.

Operative Strategy

Our surgical procedures and principles of off-pump CABG have been previously described.[11] The left-sided coronary arteries were revascularized with arterial grafts in most cases. The left anterior descending artery (LAD) was revascularized exclusively with the ITA, and the left ITA was used preferentially. The right ITA was revascularized to the LAD only when the left ITA was required to bypass a remote anastomotic site of the left circumflex artery. The most frequently used arrangement for diagonal artery and left circumflex artery was composite grafting with right ITA and radial artery. In this arrangement, the right ITA was used as an in situ graft for the diagonal, and the radial artery was anastomosed proximally to the right ITA and distally to the left circumflex artery. The right coronary artery was grafted with saphenous vein or gastroepiploic artery in most cases. Use of the gastroepiploic artery was usually limited to patients with severe stenosis of the right coronary artery. Grafts used in 242 study patients are shown in Table 2.

Aspirin (81 mg) was given to all patients before and after surgery. In 66 cases, ticlopidine hydrochloride (INN ticlopidine) was given for 1 month. Heparin (3.0 mg/kg) was administered intravenously after sternotomy, and it was neutralized at the end of the procedure with protamine sulfate (3.0 mg/kg). All radial arteries and saphenous veins were harvested open. The radial artery was soaked in a solution (20 mg olprinone plus 180 mL normal saline solution). After hemostasis was confirmed, all patients received a continuous heparin infusion until the second postoperative day. Patients with a radial artery graft received continuous administration of intravenous diltiazem during the first 24 hours after surgery.

Statistical Analysis

Continuous variables are reported as mean ± SD and categorical variables as percentages. Fisher's Exact test was used to compare categorical variables. The Mann–Whitney test was used to compare continuous variables. Actuarial and event-free survival curves were obtained with the Kaplan–Meier method. Statistical significance was calculated with the log-rank test. Multivariate analysis was performed to identify independent risk factors for arterial graft deterioration. A generalized estimating equation method was used to account for within-patient correlation. Predictors were discarded at a P value greater than .10. Covariates included in the generalized estimating equation models were graft material (ITA vs non-ITA), stenosis rate of target coronary artery (mild vs more than mild), and number of distal anastomoses from a single inflow source (single vs multiple). Target coronary artery (LAD vs non-LAD) and graft configuration (individual vs composite graft) were discarded, because LAD was grafted with ITA exclusively and composite grafting was involved in multiple grafting. Odds ratios were calculated with 95% confidence intervals. All statistical analyses were performed with SPSS statistical software (SPSS version 17.0; SPSS Japan, Tokyo, Japan).

RESULTS

Characteristics of Study Patients

The preoperative characteristics of study patients were compared with those of the patients excluded from the study (Table 3). There were significant differences between the

TABLE 1. Angiographic results for early and 1-year patencies

		Early					1 y				
			Stenosis (no.)					Stenosis (no.)			
	Distal anastomoses	Patency (%)	PP	FS	SS	CO	Patency (%)	PP	FS	SS	CO
All arteries	830	97.5%	796	13	0	21	90.8%	689	8	57	76
Internal thoracic artery											
Any	527	99.1%	512	10	0	5	96.8%	486	5	19	17
Left	292	98.6%	279	9	0	4	97.3%	279	4	1	8
Right	235	99.6%	233	1	0	1	96.2%	207	1	18	9
Radial artery	260	93.9%	242	2	0	16	78.9%	170	2	33	55
Gastroepiploic artery	43	100%	42	1	0	0	90.7%	33	1	5	4
Saphenous vein	220	96.8%	212	1	0	7	81.8%	169	10	1	40

PP, Perfectly patent; *FS*, focally stenosed; *SS*, string sign; *CO*, completely occluded.

TABLE 2. Number of distal anastomoses for each graft type according to target coronary artery

Conduit	Target coronary artery: Left anterior descending	Diagonal	Left circumflex	Right
Left internal thoracic artery				
All	198	20	60	0
Individual	167	15	39	0
Composite	31	5	21	0
Right internal thoracic artery				
All	46	104	72	0
Individual	43	23	32	0
Composite	3	81	40	0
Radial artery				
All	0	37	183	19
Individual	0	10	30	6
Composite	0	27	153	13
Gastroepiploic artery				
All	0	3	6	30
Individual	0	1	1	29
Composite	0	2	5	1
Saphenous vein				
All	0	1	17	196
Individual	0	1	11	187
Composite	0	0	6	9

groups in age, sex, and the prevalence of hypertension. Midterm clinical results were also compared between these groups (Table 3). The 2-year survival of study patients was significantly higher than that of excluded patients.

TABLE 3. Comparison of patient characteristics and midterm clinical results between study patients and excluded patients

	Study (n = 243)	Excluded (n = 280)	*P* value
Preoperative			
Age (y, mean ± SD)	66.6 ± 7.7	71.0 ± 9.3	<.001
Male (no.)	243 (86.0%)	216 (77.1%)	.01
Coronary risk factor (no.)			
Hypertension	172 (70.8%)	220 (78.6%)	.043
Diabetes	99 (40.7%)	111 (39.6%)	.858
Hyperlipidemia	153 (63.0%)	156 (55.7%)	.108
Smoking	137 (56.4%)	152 (54.3%)	.660
Old cerebral infarct (no.)	18 (7.4%)	32 (11.4%)	.137
Peripheral vascular disease (no.)	13 (5.4%)	28 (10.0%)	.052
Long-term hemodialysis (no.)	9 (3.7%)	10 (3.6%)	1.00
Midterm clinical results			
Follow-up rate (%)	100.0%	94.6%	
Follow-up period (d, mean ± SD)	654 ± 321	521 ± 408.9	<.001
Survival (%)			<.001
1 y	100.0%	95.4%	
2 y	100.0%	93.2%	
Major adverse cardiac event–free survival (%)			.897
1 y	96.3%	95.5%	
2 y	91.4%	92.9%	

Angiographic Outcomes

Arterial graft deterioration was seen in 74 patients. Patient characteristics were compared between patients with and without deterioration of grafts (Table 4). There were no differences in preoperative patient characteristics and postoperative medications between these groups.

The incidence of arterial graft deterioration was 13.8% (107/778 distal anastomoses). In univariate analysis, the incidences of graft deterioration were significantly higher for non-ITA grafts (27.7% vs 6.0%, $P < .001$), non-LAD anastomoses (19.1% vs 2.0%, $P < .001$), mild (≤75%) stenosis of target coronary arteries (26.0% vs 7.6%, $P < .001$), composite grafting (19.9% vs 7.8%, $P < .001$), and multiple anastomoses from a single inflow source (19.5% vs 5.1%, $P < .001$; Table 5). The results of multivariate analysis are shown in Table 6. Non-ITA graft, mild target stenosis, and multiple grafting from a single inflow source were the independent predictors of graft deterioration. Figure 1 shows the effects of graft configuration and number of distal anastomoses from a single inflow source on the incidence of arterial graft deterioration according to the severity of target coronary artery stenosis. The differences in the incidence of graft deterioration according to graft configurations or numbers of distal anastomoses were much greater for target arteries with mild stenosis than for those with severe stenosis. For targets with mild stenosis, composite and multiple grafting from a single inflow source resulted in a high incidence of arterial graft deterioration.

Clinical Outcomes

The recurrence of angina symptoms was significantly greater among patients with graft deterioration than among

TABLE 4. Patient characteristics and postoperative medications

	Deterioration: No (n = 169)	Yes (n = 74)	*P* value
Preoperative			
Age (y, mean ± SD)	66.7 ± 7.5	66.3 ± 8.2	.909
Male (no.)	142 (84.0%)	67 (90.5%)	.229
Coronary risk factor (no.)			
Hypertension	118 (69.8%)	54 (73.0%)	.649
Diabetes	74 (43.8%)	25 (33.8%)	.158
Hyperlipidemia	106 (62.7%)	47 (63.5%)	>.999
Smoking	91 (53.9%)	46 (62.2%)	.262
Old cerebral infarct (no.)	14 (8.3%)	4 (5.4%)	.596
Peripheral vascular disease (no.)	7 (4.1%)	6 (8.1%)	.224
Long-term hemodialysis (no.)	9 (5.3%)	0 (0%)	
Postoperative medication (no.)			
β-Blocker	72 (42.6%)	39 (52.7%)	.163
Statin	57 (33.7%)	23 (31.1%)	.767
Angiotensin-converting enzyme inhibitor	11 (6.5%)	5 (6.8%)	>.999
Angiotensin receptor blocker	35 (20.7%)	15 (20.3%)	>.999
Calcium blockade	31 (18.3%)	8 (10.8%)	.184
Warfarin	111 (65.7%)	49 (66.2%)	>.999

TABLE 5. Prevalences of arterial graft deterioration

Predictor	Total	Deteriorated	Occluded	String	*P* value
Conduit					<.001
Internal thoracic artery	500	30 (6.0%)	12 (2.4%)	18 (3.6%)	
Left	278	5 (1.8%)	4 (1.4%)	1 (0.4%)	
Right	222	25 (11.3%)	8 (3.6%)	17 (7.7%)	
Non–internal thoracic artery	278	77 (27.7%)	41 (14.8%)	36 (13.0%)	
Radial artery	239	69 (28.9%)	38 (15.9%)	31 (13.0%)	
Gastroepiploic artery	39	82 (0.5%)	3 (7.7%)	5 (12.8%)	
Target coronary artery					<.001
Left anterior descending	244	5 (2.0%)	3 (1.2%)	2 (0.8%)	
Non–left anterior descending	534	102 (19.1%)	50 (9.4%)	52 (9.7%)	
Diagonal	164	19 (11.6%)	9 (5.5%)	10 (6.1%)	
Left circumflex	321	74 (23.1%)	36 (11.2%)	38 (11.8%)	
Right	49	9 (18.4%)	5 (10.2%)	4 (8.2%)	
Stenosis of target coronary artery					<.001
More than mild (>75%)	516	39 (7.6%)	19 (3.7%)	20 (3.9%)	
Mild ≥75%	262	68 (26.0%)	34 (13.0%)	34 (13.0%)	
Graft configuration					<.001
Individual	396	31 (7.8%)	15 (3.8%)	16 (4.0%)	
Composite	382	76 (19.9%)	38 (9.9%)	38 (9.9%)	
No. of distal anastomoses from single inflow source					<.001
1	16	312 (5.1%)	6 (1.9%)	10 (3.2%)	
≥2	466	91 (19.5%)	47 (10.1%)	44 (9.4%)	
2	173	31 (17.9%)	18 (10.4%)	13 (7.5%)	
3	206	39 (18.9%)	14 (6.8%)	25 (12.1%)	
4 or 5	87	21 (24.1%)	15 (17.2%)	6 (6.9%)	

All data represent numbers of grafts.

those without graft deterioration (9.5% vs 3.0%, $P = .049$). The incidence of major adverse cardiac events tended to be higher among patients with graft deterioration, but the difference was not statistically significant (13.5% vs 6.5%, $P = .104$).

DISCUSSION

Arterial Graft Deterioration

In this study, we focused on arterial grafts that had been patent immediately after surgery and became occluded or diffusely narrowed during the first postoperative year. Most previous studies have used patency rate as an index of the graft function, and the patency rates in our study were comparable with those in previous studies.[12,13] We also treated string sign as graft dysfunction, and the incidence of string sign was nearly identical to that of graft occlusion. There is still some debate whether graft occlusion and string sign have to be viewed in a similar manner. It was sometimes difficult to discriminate clearly between grafts showing string sign and those showing occlusion, however, because some grafts appeared to be intermediate between these states. Graft occlusion and string sign were sometimes intermingled in the same graft, and some grafts were halfway patent, showing string sign and occlusion in the latter half. Moreover, the prevalence and predictors were nearly identical for graft occlusion and string sign. In this study, string sign and graft occlusion were therefore similarly viewed as evidence of a deteriorated graft.

TABLE 6. Results of multivariate analysis

Predictor	Odds ratio	95% Confidence interval	*P* value
Non–internal thoracic artery graft	5.05	2.79–9.13	<.001
Mild target stenosis	4.52	2.77–7.37	<.001
Multiple grafting from single inflow source	2.68	1.37–5.25	.004

Predictors of Graft Deterioration

Our study revealed several predictors of arterial graft deterioration 1 year after CABG. Mild stenosis of the target coronary artery was an independent predictor of graft deterioration. Other studies have also shown mild stenosis to be an independent predictor of graft occlusion[8] or string sign.[14,15] Graft material was also an independent predictor. Radial artery and gastroepiploic artery were more susceptible to graft deterioration. The susceptibilities of various graft materials to graft occlusion or string sign have not yet been fully determined, but in our study ITA grafts were apparently resistant to graft deterioration. Multiple grafts originating from a single inflow source were susceptible to graft deterioration. In this study, complex design, such as

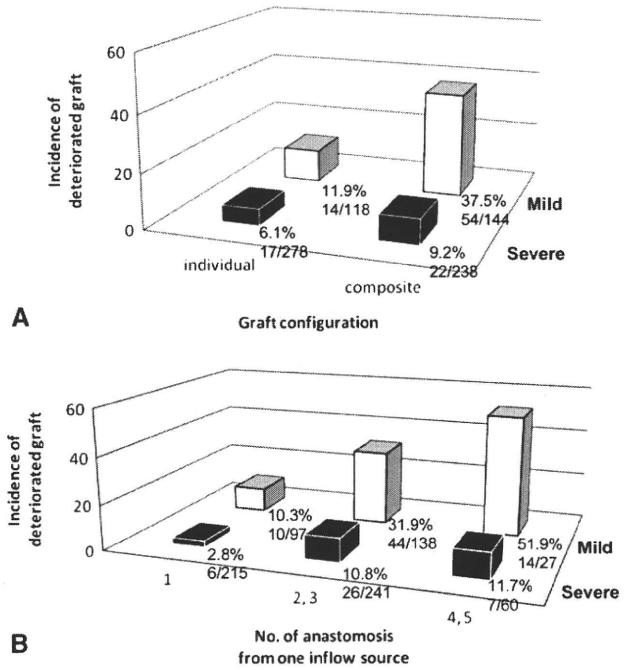

FIGURE 1. Effects of graft configuration (A) and number of distal anastomoses from single inflow source (B) on incidence of arterial graft deterioration according to severity of target coronary artery stenosis.

composite grafting and sequential multiple grafting, appeared to have certain pitfalls, although several studies have reported excellent patency rates for such grafts.[16,17] When planning these types of grafts, selection of the target coronary artery is considered extremely important. For the target with mild stenosis, these types of grafts would result in a high failure rate, and individual grafts should be selected instead. This finding is in agreement with a previous study[18] that demonstrated reduced blood flow in a composite graft used for a less stenosed target. On the other hand, patient characteristics and postoperative medications were not related to graft deterioration. These results enhance the importance of graft design in the prevention of graft deterioration in multiple arterial revascularization procedure.

Clinical Significance of Graft Deterioration

There is no consensus regarding the clinical significance of graft deterioration, especially of a graft showing string sign. There have been several case studies[19,20] in which arterial grafts showing string sign regained patency after progression of native coronary artery stenosis. Furthermore, arterial grafts showing string sign can increase graft flow in response to a hyperemic situation, which suggests the capacity to meet the blood flow demand and to function as a bypass conduit.[21,22] Several studies, however, have suggested poor angiographic outcomes of grafts showing string sign. Kim and colleagues[12] reported that among 20 grafts initially FitzGibbon grade B, 12 grafts remained grade B and 3 grafts were occluded 3 years after surgery. Nakajima and coworkers[7] reported that 71.4% of the bypasses with competitive or reversed flow at early angiography were occluded 3 years after surgery. Our study revealed that patients with deteriorated grafts were more likely to have ischemic symptoms. There have been no reports investigating the long-term consequences of grafts showing string signs, and further investigation is required.

Mechanism of Graft Deterioration

The mechanism of arterial graft deterioration is suggested by several previous studies. Arterial remodeling is a well-known physiologic adaptation that occurs in response to long-term changes in blood flow to normalize shear stress.[23] For ITA grafts, animal studies have demonstrated that a low-flow condition results in a decreased diameter of the artery accompanied by medial thickening within several months.[24] These findings suggest that the deterioration of an arterial graft may be induced by a low-flow condition, and several clinical studies supported this hypothesis. Akasaka and associates[21] investigated the flow dynamics of the ITA graft showing string sign by use of a Doppler guide wire and demonstrated to and fro signals with systolic reversal and diastolic antegrade flow. Shimizu and coworkers[25] demonstrated decreased graft diameter in a graft with low-flow condition. Tokuda and colleagues[26] reported that a lower mean graft flow and a higher percentage of backward flow as measured by intraoperative transit time flow were independent risk factors for arterial graft deterioration. The results of our study are in agreement with these findings. Graft designs that might decrease the flow at distal anastomoses were revealed to be risk factors for arterial graft deterioration. Mild stenosis of the target coronary artery promotes flow competition. Multiple grafting from a single inflow source may limit the inflow volume and result in decreased graft flow. These findings suggest that a certain amount of graft flow is required to maintain the function of the arterial graft.

Study Limitations

This study has several limitations. First, all data were retrospectively collected, which may have led to information bias. Second, follow-up angiography was performed for only 47.8% of the patients who underwent off-pump CABG during this study period. Angiography was performed according to a protocol and was not symptom directed. We cannot eliminate the possibility that there was a bias in the patient selection. The patient characteristics and the midterm clinical results are compared between the study patients and the excluded patients in Table 3. The differences need to be considered in the interpretation of our data. Importantly, the survival of the study patients was significantly higher than that of the excluded patients. This finding suggests that the rate of arterial graft deterioration may have been understated in our cohort, which was biased

toward healthier patients. Third, the study patients included those with arterial grafts showing focal stenosis (11 instances of distal stenosis in 9 patients) on early angiography. The 11 grafts with focal stenosis seemed to have good graft flow on early angiography. At 1-year angiography, stenosis had disappeared in 5 grafts, and 6 grafts continued to show focal stenosis. None of the grafts with focal stenosis had graft deterioration. Fourth, the use of secondary preventive medication in the study patients was relatively low. Although postoperative medication was not statistically associated with the development of graft deterioration, it is possible that this low use of secondary prevention medication enhanced the development of graft deterioration.

CONCLUSIONS

Arterial graft deterioration 1 year after CABG occurred in 13.8% of all distal anastomoses in arterial grafts. The graft deterioration was closely related to particular graft materials and designs. The incidence of graft deterioration was higher for non-ITA grafts, non-LAD anastomoses, mild ($\leq$75%) stenosis of target coronary arteries, composite grafting, and multiple anastomoses from a single inflow source. The incidence was particularly high when composite or multiple grafting from a single inflow source was performed to a target coronary artery with mild stenosis. When performing multiple arterial grafting, careful attention to the selection of graft material and design is important to gain the full advantage of arterial grafts.

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ORIGINAL ARTICLE

Comparison of the waveforms of transit-time flowmetry and intraoperative fluorescence imaging for assessing coronary artery bypass graft patency

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Abstract
Purpose. An intraoperative fluorescence imaging (IFI) system, which can provide visual images, could be the common method for assessing graft patency intraoperatively. We conducted a prospective comparison of the diagnostic accuracy of both the fast Fourier transformation (FFT) analysis of transit-time flowmetry (TTFM) waveform and the IFI system to determine graft failure.
Methods. The study included 10 saphenous vein grafts (SVGs), all of which were aortocoronary grafts. Each patient underwent isolated coronary artery bypass grafting (CABG), including conventional CABG or off-pump CABG, and then underwent X-ray angiography after CABG. When intraoperative hemodynamics had stabilized, the grafts were evaluated with both the IFI system and TTFM. Based on the obtained flow profile of TTFM, certain variables were calculated. The waveforms of TTFM were analyzed with the FFT series. Harmonic distortion (HD) was calculated from the amplitudes, and the fundamental frequency was thus determined using the FFT series.
Results. The IFI system demonstrated a satisfactory flow of all grafts. X-ray angiography demonstrated that one SVG was 75% stenosed, and the others were patent. The mean graft flow (MGF) and the pulsatility index (PI) of the patent SVGs were not significantly different from those of the stenosed SVG. The HD of the patent SVGs was significantly different from that of the stenosed SVG.
Conclusion. The HD of the TTFM waveform can provide better diagnostic accuracy for detecting clinically significant grafts than MGF and PI of TTFM and the IFI system.

Key words Coronary artery bypass grafting · Ultrasound · Imaging · Ischemic heart disease

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Introduction

Graft failure is associated with several adverse consequences such as perioperative myocardial infarction, a need for repeated intervention, and symptoms. Early graft failure is a major cause of cardiac morbidity and mortality after coronary artery bypass grafting (CABG), occurring in up to 3% of grafts (8% of patients).[1] It is the common cause of perioperative myocardial infarction, which is detectable in up to 9% of patients before hospital discharge.[2] Postoperative angiography, used to assess graft patency before hospital discharge, has resulted in reoperation in some patients.[3,4]

Consequently, several techniques have been employed to assess intraoperative graft patency. These have included electromagnetic study,[5] transit-time flowmetry (TTFM),[6] Doppler velocity waveform,[7] epicardial echocardiography,[8] and conventional[9] and thermal[10] coronary angiography techniques. All techniques have limitations and frequently provide indirect or poor-resolution definition of grafts and flow. Recently, it was reported that the intraoperative fluorescence imaging

(IFI) system could evaluate the patency of bypass grafts[11] and that it provided better diagnostic accuracy for detecting clinically significant graft failure than does TTFM.[12] However, it has some limitations. First, it is not quantitative. Second, it does not allow precise definition of anastomotic quality. Finally, it is useful only with a skilled operator to estimate the quality of grafts.

We have previously reported that when using a fast Fourier transformation (FFT) analysis the waveform of TTFM was useful for estimating the quality of grafts.[13] Therefore, we describe our preliminary experience with analysis of the waveform of TTFM using FFT compared with the IFI system.

Material and methods

The IFI system (SPY; Novadaq Technologies, Toronto, Canada) is based on the fluorescence properties of indocyanine green (ICG). When illuminated with 806-nm light, ICG fluoresces and emits light at 830 nm. This fluorescent light is captured by a charged couple device (CCD) video camera at 30 frames per second and displayed on a computer monitor. The imaging head is positioned over the exposed heart, and the laser is activated before the first pass of a bolus of ICG through the field of view. After analyzing the sequence, the images are saved to the computer in audio-video interleave movie format.

Six patients underwent isolated CABG, including one with conventional CABG and five with off-pump CABG; all had postoperative coronary angiography. The patients received 10 saphenous vein grafts (SVGs) and 8 internal thoracic arteries (ITAs). The SVGs were aorto-coronary bypass grafts, and the ITAs were in situ grafts. All of the anastomoses were performed by one surgeon (Y.O.) in the same fashion.

Graft flow tracing was obtained intraoperatively using a transit-time flowmetry (BF 1000; Medi-Stim AS, Oslo, Norway). This machine is to be able to measure graft flow and directly calculate a power of harmonics from the waveform of the flow using FFT. A flow probe to fit each SVG or ITA (between 3 and 4 mm) was placed around the graft when the hemodynamic condition had stabilized after the cardiopulmonary bypass was weaned, and all grafts were anastomosed.

Based on the obtained flow profile, the following variables were calculated: mean graft flow (MGF), pulsatility index (PI), and FFT of the flow waveform. The theoretical basis and the procedure for TTFM measurement have already been reported.[13] Harmonics of FFT analysis by the flowmeter existed at frequencies that were multiples of the frequency of the original waveform and were described in terms of amplitude and phase (Fig. 1A). In the present study, we defined F_0 as a power of the fundamental frequency, H_1 as a power of the first harmonic, H_2 as a power of the second harmonic, and so on for H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10} (Fig. 1B). Ha (= $H_5 + H_6 + H_7 + H_8 + H_9 + H_{10}$) was then calculated.

After completion of the distal coronary artery anastomosis, 1 ml of ICG dye was injected through the central venous line and flushed through with 5 ml of natural saline. Screening was started at the time of injection and continued throughout them. Images were then recorded on a computer hard drive. The procedure takes 3–4 min per anastomosis. Images were assessed offline to determine surgeon-specified image quality and

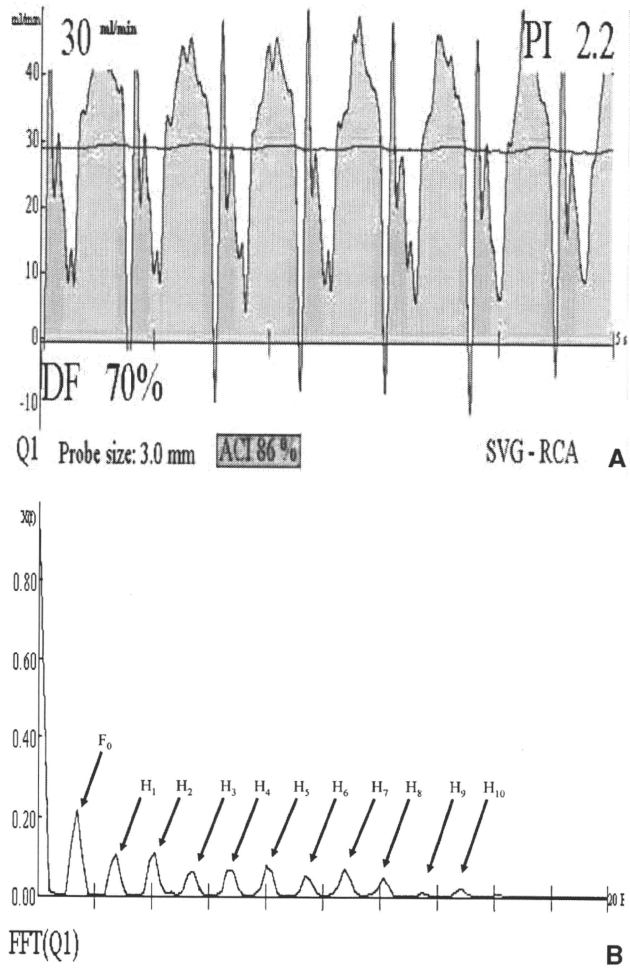


Fig. 1 **A** Typical waveform of a saphenous vein graft (SVG) (aorto-coronary bypass). This graft was deemed to be patent on X-ray angiography after coronary artery bypass grafting (CABG). *RCA*, right coronary artery; *DF*, diastolic filling; *PI*, pulsatility index; *ACI*, acoustic insufficiency. **B** Typical power spectrum of the waveform (**A**) of SVG using a fast Fourier transform (*FFT*) analysis. We defined F_0 as a power of the fundamental frequency, H_1 as a power of the first harmonic, H_2 as a power of the second harmonic, and so on for H_3, H_4, H_5, H_6, H_7, H_8, H_9, and H_{10}

interrater agreement. The IFI system was used on all grafts. All patients underwent X-ray coronary angiography 1–2 months after leaving the hospital.

All data are expressed as the mean ± SD. The data were compared using the Grubbs-Smirnov test. $P < 0.05$ was considered statistically significant.

Results

All patients experienced an uneventful postoperative course. Intraoperative graft flow was visualized in all grafts, including SVGs and ITAs, confirming patency by an IFI system. Then, all grafts were patent in the operating room by an IFI system. In all patients, X-ray angiography was performed at a mean of interval 44.8 ± 13.7 days after CABG. One SVG, which went from the aorta to the no. 4 posterior descending branch, was deemed to be 75% occluded on X-ray angiography. Other grafts were patent.

The SVG was demonstrated to be patent with the IFI system in the operating room (Fig. 2A). However, the SVG was found to be 75% occluded with X-ray angiography after CABG (Figure 2B). The Ha of this graft was significantly higher than that of the other SVGs ($P < 0.05$) (Fig. 3). The MGFs and PIs of this graft were not significantly different from those of the other SVGs (Fig. 4).

All ITA grafts were deemed to be patent with the IFI system and X-ray angiography. There was no significant difference in the Ha, MGF, or PI among all ITA grafts.

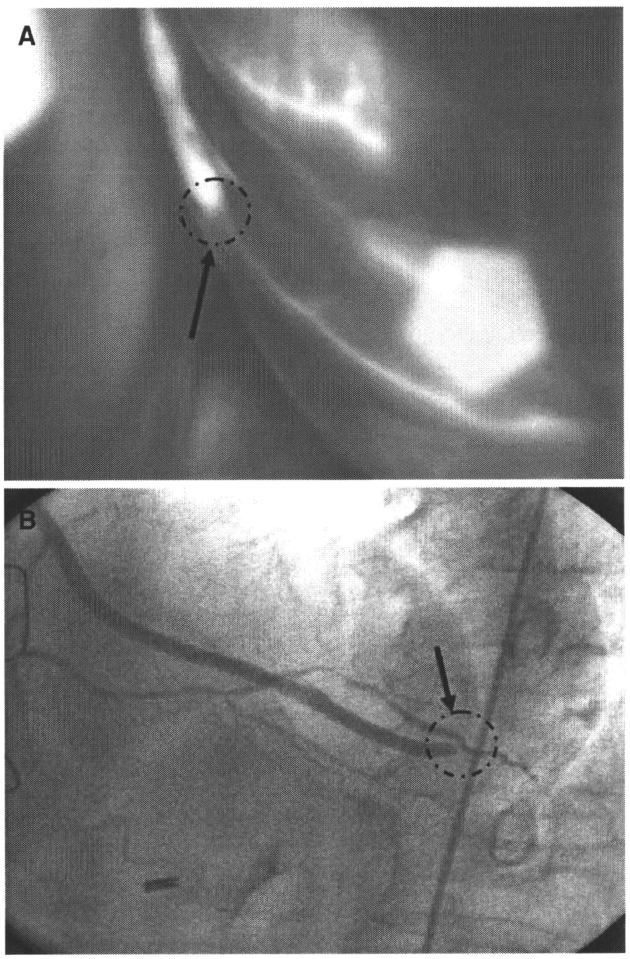


Fig. 2 **A** Intraoperative fluorescence imaging (IFI) system reveals patency of the SVG to the no. 4 posterior descending branch (PD) at the anastomosis. The IFI system captured the proximal coronary open. *Arrow* shows the anastomosis in the *circle*. **B** After CABG, angiography reveals stenosis of the SVG to the no. 4 PD at the anastomosis. *Arrow* shows the anastomosis in the circle

Discussion

We demonstrated that the waveform of TTFM might be more useful than the IFI system for estimating the quality of grafts. In our estimation, graft assessment of the TTFM waveform using FFT analysis suggested stenosis, whereas the IFI system did not.

Among graft assessment techniques currently available, contrast X-ray coronary angiography remains the gold, or reference, standard. Hybrid operating rooms with either ceiling-mounted or floor-mounted angiography equipment are becoming a reality owing to the advances in percutaneous and minimal access valvular surgery and endovascular surgery. This room is not yet popular, however. It is generally not available in the cardiac operating room because of logistical difficulties incorporating bulky equipment and safety concerns regarding contrast-induced renal insufficiency and aortoembolic and bleeding complications.[14] Although graft patency assessment techniques such as thermal angiography, Doppler flow measurement, and electromagnetic flow measurement have been attempted in the operating room, such techniques generally do not provide high-fidelity angiographic information and have not gained implementation in routine surgical practice.[5,9,15–17]

Our previous article noted that using FFT analysis the waveform of TTFM was useful for estimating the quality of grafts.[13] In this study, we indicated that the waveform of the occluded grafts had more high-frequency components than did the waveform of patent grafts. In the present study, the power of Ha in the patent grafts was lower than that in the stenotic graft. The powers of Ha are components of a high-frequency TTFM waveform. Thus, we demonstrated that Ha could be an index for assessing the quality of grafts in the future.

Some authors have reported that the IFI system provides better diagnostic accuracy for detecting graft errors

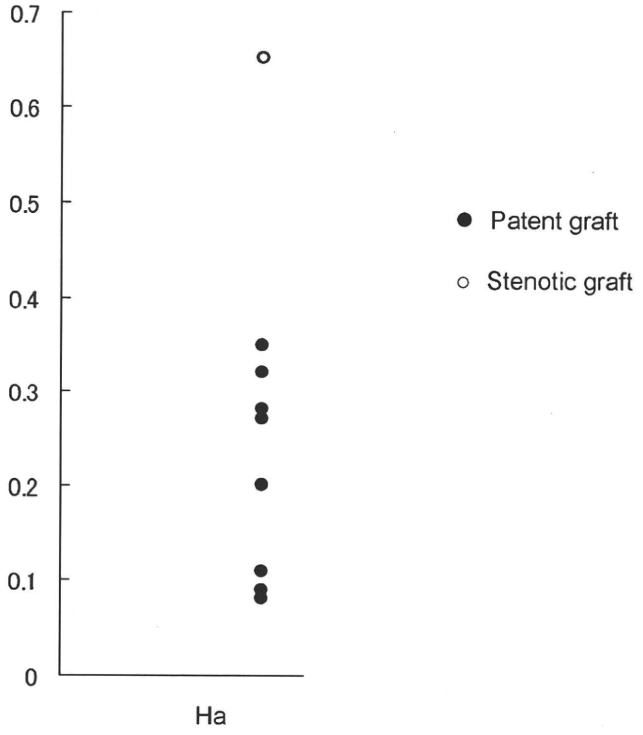
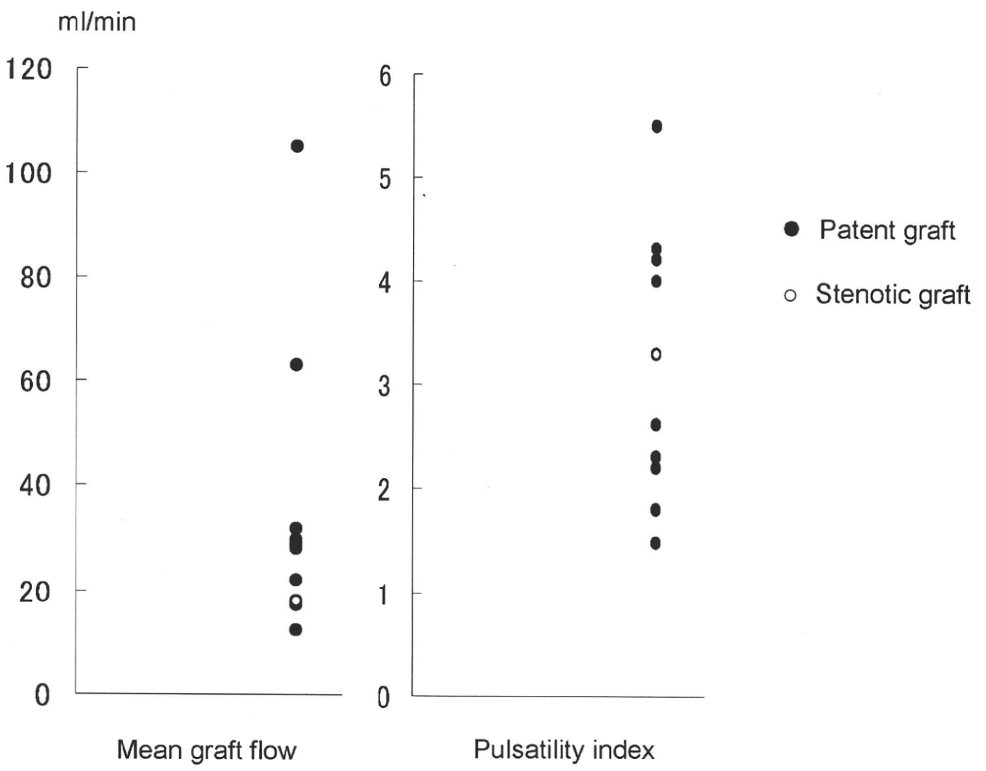


Fig. 3 The Ha (= $H_5 + H_6 + H_7 + H_8 + H_9 + H_{10}$) of this graft was significantly higher than that of the other SVGs ($P < 0.05$). *Filled circles*, patent SVGs; *open circles*, 75% stenosis of the SVG at the anastomosis

than does TTF[11,12,18] and that the limitation of wider use of TTF technology has been the lack of clear-cut values.[19,20] However, the IFI system is dependent on the surgeon's skill and the method for injecting ICG to assess the quality of grafts. It is sometimes difficult to detect anastomosis of coronary arteries behind the heart (e.g., right coronary distal branches or left circumflex distal branches) using the IFI system. Furthermore, the technique allows precise definition of the quality of the anastomosis in only about three-fourths of grafts. This is because the depth of penetration of the laser beam is only around 1 mm, which therefore precludes is use for greater depths of the native coronary artery. For the same reason, pedicled conduits are less well visualized than skeletonized ones.[11] The view with the IFI system could not be determined objectively. In contrast, the method using TTFM is easy to handle, not time-consuming, minimally invasive, easily meaningful and objective, and relatively inexpensive. However, the site of graft failure cannot be detected using TTFM, whereas the IFI system can detected it. Perhaps, the best method to assess graft quality should be a combined TTFM and IFI system.

This study was a preliminary one to compare a new technique using FFT and the IFI system in a small number of patients. It is a first report to compare our method with IFI system. In this study and the study we

Fig. 4 Mean graft flow and pulsatility index of this graft were not significantly different from those of the other SVGs. *Filled circles*, patent SVGs; *open circles*, 75% stenosis of the SVG at the anastomosis



reported elsewhere,[13] the cutoff values were unclear. We need to increase the number of cases and investigate such problems as whether the kind of graft (e.g., venous or arterial grafts; in situ or free grafts; grafts to the left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) affects the waveform of the graft and the cutoff values.

Conclusion

We compared the waveforms of TTFM with the view of IFI system for assessing CABG graft patency. We demonstrated that the waveform of TTFM using FFT analysis could be more useful than the IFI system for assessing the quality of the graft. We also found that the Ha value was higher in nonpatent grafts, including occluded or stenotic grafts, than that in patent grafts. This study was a pilot study. We need to increase the number of patients examined with the FFT and IFI system.

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Serum 1,5-anhydro-D-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study

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ABSTRACT

Objective: Serum 1,5-anhydro-D-glucitol (1,5-AG) is well-known to be a useful clinical marker of both short-term glycemic status and postprandial hyperglycemia. In addition, previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test is a risk factor for cardiovascular diseases (CVD). However, no previous prospective study has reported the association between serum 1,5-AG levels and the risk of CVD. In this study, we examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD.

Methods: Our study was a population-based cohort study in an urban area of Japan. Study subjects comprised 2095 initially healthy Japanese (991 men and 1104 women, mean age: 58.5 years) with no history of coronary heart disease (CHD) or stroke. They were followed up for an average of 11.1 years, and 147 CVD events (64 CHD and 83 strokes) were observed.

Results: The adjusted hazard ratios (HRs) of all CVD in men increased linearly ($p = 0.004$). The HR in the category with serum 1,5-AG levels of 14.0 μg/mL or less was 2.22 (95% confidence interval; 1.24–3.98) compared to the reference category (24.5 μg/mL or greater). Similar results were also shown with a sensitivity analysis in non-diabetic men. Conversely, no significant relationship between serum 1,5-AG levels and CVD risks was observed in women.

Conclusions: Our results suggest that measurement of serum 1,5-AG levels is useful to detect individuals, especially men, at higher risk for CVD, regardless of the presence or absence of diabetes.

1. Introduction

Serum 1,5-anhydro-D-glucitol (1,5-AG) levels are well-known to rapidly decrease concomitantly with the excretion of glucose in urine, and serum 1,5-AG is a useful clinical marker for short-term glycemic status and postprandial hyperglycemia [1–3].

Previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test (OGTT) is a risk factor for cardiovascular diseases (CVD) [4,5]. A randomized controlled trial of individuals with impaired glucose tolerance also reported that acarbose, an α-glycosidase inhibitor that suppresses the elevation of postprandial glucose levels, reduced the incidence of CVD as well as type 2 diabetes [6]. These findings suggest that detection and improvement of postprandial hyperglycemia is important for CVD prevention.

An OGTT is useful for the detection of postprandial hyperglycemia, however, it requires overnight fasting, long time, additional costs, and is not always feasible in routine clinical settings or during health check-ups. In contrast, measurement of serum 1,5-AG levels can be performed using a single non-fasting blood sample, relatively costs less, and may be an alternative to OGTT. However, to our knowledge, no previous prospective study has shown the association between serum 1,5-AG levels and the risk of CVD in initially healthy individuals. We examined whether serum 1,5-AG levels can predict the incidence of first-ever CVD in a population-based cohort study of an urban area in Japan.

2. Methods

2.1. Study design and samples

The details of the Suita study have been described elsewhere [7–9]. Briefly, the Suita study is a prospective population-based cohort study of an urban area in Japan. In 1989, 6485 Suita city residents (age, 30–79 years) were randomly sampled and enrolled as study participants. They underwent medical examinations every 2 years. Among these participants, 2406 participants underwent medical examinations between April 1994 and February 1995, and their serum samples were collected and stored at −80 °C. In this

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study, we measured serum 1,5-AG levels in these stored samples. Of these 2406 participants, 289 were excluded from the present analysis for the following reasons: history of coronary heart disease (CHD) or stroke ($n=78$), lost to follow-up ($n=132$), serum creatinine level of 176.8 mmol/L (2.0 mg/dL) or more ($n=4$), and data missing ($n=97$). Finally, the remaining 2095 participants (991 men and 1104 women) with serum 1,5-AG measurements were included as subjects in the baseline study and were followed up until December 31, 2007. Informed consent was obtained from all subjects, and the institutional review board at the National Cerebral and Cardiovascular Center approved this study.

2.2. Baseline data collection

The baseline survey included questionnaires, anthropometric measurements, and blood sample tests. Height and weight were measured in light clothing, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Blood pressure was measured 3 times in more than 1-min intervals by well-trained physicians in a sitting position after at least 5 min of rest, using a standard mercury sphygmomanometer [7], and the third measurement of blood pressure was adopted for the present analyses. The levels of total serum cholesterol, high-density-lipoprotein (HDL)-cholesterol and creatinine were determined using an automatic analyzer in the laboratory of the National Cerebral and Cardiovascular Center. Estimated glomerular filtration rates (eGFR) were estimated with a following equation for the Japanese: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (×0.739: if women) [10].

2.3. Measurement of 1,5-AG

In 2009, stored frozen serum samples were shipped to the clinical laboratory company for measurement of 1,5-AG (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). 1,5-AG was measured using the enzymatic method with the "Determiner L 1,5-AG" measurement kit manufactured by the Kyowa Medex Co., Ltd. (Tokyo, Japan) and an H7700 Clinical auto-analyzer, manufactured by the Hitachi High-Technologies Corporation (Tokyo, Japan). The coefficient of variation was less than 5%.

2.4. Ascertainment of outcomes

Outcome ascertainment has been previously described elsewhere [7–9]. The main outcome is the incidence of first-ever CVD events (stroke and CHD). Physicians or nurses checked the health status of each subject at biennial clinical visits to the National Cerebral and Cardiovascular Center, and all participants also completed yearly questionnaires by either mail or telephone. The patients suspected of developing stroke or CHD were confirmed by a review of medical records performed by either the registered hospital physicians or the cohort study research physicians. In addition, to complete the surveillance, we also conducted a systematic search of death certificates for fatal stroke and MI. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labor and coded for the National Vital Statistics.

A stroke was defined according to criteria from the US National Survey of Stroke [11]. Classification of stroke subtypes (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) was based on the examination of computed tomographic scans, magnetic resonance images, or autopsies (subarachnoid hemorrhages were excluded from the present analyses). With regard to myocardial infarction (MI), definite and probable MI were defined according to the criteria of the MONICA project [12]. The criteria for CHD were first-ever MI, coronary angioplasty, coronary artery bypass grafting and sudden cardiac death.

2.5. Statistical analysis

A previous report from Japan proposed a serum 1,5-AG level of 14.0 μg/mL, irrespective of sex, as the cut-off for the diagnosis of diabetes [13]. The distribution of serum 1,5-AG levels differed between sexes. Accordingly, we adopted a serum 1,5-AG level of 14.0 μg/mL as the lower cut-off in common, and set the median of those who had serum 1,5-AG of more than 14.0 μg/mL as the upper cut-off (overall and according to sex), overall: 23.1 μg/mL, men: 24.5 μg/mL, women: 21.3 μg/mL. These cut-offs were used to compare baseline characteristics, crude incidence rates, and hazard ratios (HRs). To calculate p values for continuous variables, one-way analysis of variance was used, and for categorical variables, Chi-square test was used. To compare in women the prevalence of medication for diabetes and current alcohol drinking status, Fisher's exact test was used. The p values to test for a linear trend in HRs were calculated.

A Cox proportional hazard model was used to estimate age- and multivariate-adjusted HRs with 95% confidence intervals (CIs). The HRs were adjusted for the following baseline covariates as follows for model 1, age; for model 2, model 1 plus BMI, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication), hypercholesterolemia (total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication) [14], HDL-cholesterol, eGFR, current cigarette smoking (non-current and current) and current alcohol drinking (men; non-current/light to moderate/heavy, women: non-current/current);, for model 3, model 2 plus diabetes (fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), postprandial plasma glucose (PPG) ≥11.1 mmol/L (200 mg/dL), or use of anti-diabetic medication). Fasting was defined as fasting time of 8 h or more ($n=1401$, 67%), and postprandial was defined as that of less than 8 h ($n=694$, 33%). We defined current alcohol drinking as non-current drinking, light to moderate drinking (alcohol consumption of less than 46 g/day), or heavy drinking (that of 46 g/day or more). However, because women with heavy alcohol drinking were few ($n=8$, 0.7%) and had no CVD incidence, we treated current alcohol drinking as non-current/current drinking in the multivariate analyses of women. Menopause was added to model 2 and model 3 in women. Combined analyses of women and men adjusting for sex were conducted only in CHD and ischemic strokes because significant interactions between sex and serum 1,5-AG levels were observed in all CVD ($p=0.03$) and all strokes ($p=0.01$).

In addition, three sensitivity analyses were conducted: First, similar analyses were performed in non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL). Second, the definition of postprandial in the diagnostic criteria for diabetes was changed to a fasting time of 2 h or less (postprandial: $n=28$, 1%), and similar analyses were conducted to confirm the influence of diabetes diagnostic criteria by PPG. Third, adjustment for waist circumferences in model 2, instead of BMI, was conducted to estimate the influence of insulin resistance. We did not enter both BMI and waist circumferences into the models to avoid the colinearity problem because waist circumferences highly correlated with BMI (correlation coefficient: 0.84). In addition, triglycerides levels were categorized by tertile and added to the model 2 in the combined analysis of women and men with fasting time of 8 h or more ($n=1401$), and similar analyses for CHD and ischemic strokes were conducted.

All p values were two-tailed, and $p<0.05$ was considered statistically significant. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, Carolina, USA).

3. Results

The mean (standard deviation) of serum 1,5-AG was 23.0 μg/mL (9.2) in men and 20.0 μg/mL (7.0) in women. The overall dis-

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Table 1
Baseline characteristics by sex and serum 1,5-anhydro-D-glucitol levels, the Suita study, Japan, 1994–2007.

	Men			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	423	416	152	
Age (years)	58 (12)	61 (12)	63 (11)	<0.001
Body mass index (kg/m^2)	22.7 (2.7)	22.8 (2.9)	23.1 (2.9)	0.24
HDL cholesterol (mmol/L)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.48
1,5-Anhydro-D-glucitol (μg/mL)	31.3 (5.6)	19.7 (3.0)	8.8 (3.6)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (15.6)	78.1 (16.0)	79.0 (18.1)	0.19
Hypertension (%)[a]	32	37	45	0.01
Hypercholesterolemia (%)[b]	23	23	21	0.85
Diabetes (%)[c]	0	3	30	<0.001
Current cigarette smoking (%)	44	39	41	0.36
Alcohol drinking (non/light to moderate/heavy) (%)	29/53/18	29/55/16	35/47/18	0.55
Hypertension medication (%)	13	15	20	0.09
Hypercholesterolemia medication (%)	4	4	5	0.81
Diabetes medication (%)	0	0	20	<0.001
	Women			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥21.3	14.1–21.2	≤14.0	
Number of subjects	442	438	224	
Age (years)	59 (12)	55 (12)	58 (12)	<0.001
Body mass index (kg/m^2)	22.2 (3.2)	21.9 (2.7)	22.3 (3.2)	0.12
HDL cholesterol (mmol/L)	1.6 (0.4)	1.6 (0.3)	1.6 (0.3)	0.001
1,5-Anhydro-D-glucitol (μg/mL)	26.7 (4.1)	18.0 (2.0)	10.5 (3.2)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (19.7)	81.2 (16.8)	81.1 (15.2)	0.71
Hypertension (%)[a]	33	26	31	0.06
Hypercholesterolemia (%)[b]	39	37	38	0.80
Diabetes (%)[c]	1	1	12	<0.001
Current cigarette smoking (%)	11	8	8	0.42
Current alcohol drinking (non/light to moderate/heavy) (%)	75/25/0	72/27/1	72/28/0	0.31
Menopause (%)	76	63	71	<0.001
Hypertension medication (%)	14	12	17	0.17
Hypercholesterolemia medication (%)	7	7	5	0.46
Diabetes medication (%)	0	0	4	<0.001

Mean (standard deviations), or percentage is shown. GFR means glomerular filtration rate.
[a] Hypertension is defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.
[b] Hypercholesterolemia is defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication.
[c] Diabetes is defined by fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) in those with fasting time of 8 h or more, postprandial plasma glucose ≥11.1 mmol/L (200 mg/dL) in those with fasting time of less than 8 h, or the use of antidiabetic medication.

tribution (minimum, 25th percentile, median, 75th percentile, maximum) of serum 1,5-AG by sex was 1.2, 17.0, 23.1, 28.9, and 55.3 μg/mL, respectively in men, and 1.7, 15.2, 19.8, 24.8, and 41.5 μg/mL, respectively in women (data not shown). The prevalence of diabetes and medication for diabetes at baseline was highest in the category with the lowest serum 1,5-AG (≤14.0 μg/mL) in both sexes, and was much higher in men (Table 1). Age and prevalence of hypertension increased as serum 1,5-AG decreased in men only.

During the follow-up period (11.1 years average), 147 CVD events (64 CHD and 83 strokes) were observed. The CHD included 14 percutaneous coronary angioplasty, 5 coronary artery bypass grafting, 1 sudden death, 41 myocardial infarctions and 3 unclassified CHD. The strokes included 53 ischemic strokes, 14 hemorrhagic strokes and 16 unclassified strokes. The incidence rates of all CVD and each CVD subtype increased as 1,5-AG levels decreased in men, and the incidence rate of all CVD was 15.1 per 1000 person-years in the lowest 1,5-AG category (Table 2). In model 2, there was a statistically significant linear increase in the adjusted HRs of all CVD in men ($p = 0.004$), and the adjusted HR was 2.22 (95% CI 1.24–3.98) in the lowest 1,5-AG category. In model 3, the adjusted HR of all CVD in the lowest 1,5-AG category was less than model 2. However, the adjusted HR of the middle category (14.1–24.4 μg/mL) was not very different and the elevation of risk was still significant, 1.74 (95% CI 1.07–2.84). In men, similar results were observed for each CVD subtype, although the HRs of CHD were much lower than of all strokes and were not statistically significant. In women, similar results were not observed, although, for CHD, similar trends were observed (Table 3). In the combined analysis of women and men for CHD, the HRs in model 2 increased linearly with decrease in serum 1,5-AG levels ($p = 0.03$), and the adjusted HR in the lowest 1,5-AG category was 2.10 (95% CI 1.10–4.02) (Table 4).

A sensitivity analysis for non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL) showed that the adjusted HRs for all CVD in model 2 increased as 1,5-AG levels decreased ($p = 0.03$), and the adjusted HR was 2.00 (95% CI 0.88–4.55) in the lowest 1,5-AG category (Table 5). Similar results were observed with all strokes and ischemic strokes, but such a relationship was not clear in CHD.

In the sensitivity analyses, altering the definition of postprandial, entering waist circumferences or adding triglycerides levels to the models hardly alter the results. In addition, waist circumferences or triglycerides levels were not related with the risk for CVD or each CVD subtype.

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Table 2
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in men, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Person-years	4727	4322	1455	
All cardiovascular diseases				
Cases, *n*	26	49	22	
Incidence rates/1000 person-years	5.5	11.3	15.1	
Model 1[a]	1	1.76 (1.09–2.86)	2.29 (1.29–4.07)	0.003
Model 2[a]	1	1.79 (1.10–2.91)	2.22 (1.24–3.98)	0.004
Model 3[a]	1	1.74 (1.07–2.84)	1.72 (0.89–3.34)	0.049
Coronary heart disease				
Cases, *n*	16	19	10	
Incidence rates/1000 person-years	3.4	4.4	6.9	
Model 1[a]	1	1.21 (0.61–2.38)	1.81 (0.81–4.05)	0.17
Model 2[a]	1	1.14 (0.57–2.25)	1.59 (0.70–3.59)	0.29
Model 3[a]	1	1.13 (0.57–2.24)	1.47 (0.59–3.68)	0.44
All strokes				
Cases, *n*	10	30	12	
Incidence rates/1000 person-years	2.1	6.9	8.2	
Model 1[a]	1	2.56 (1.25–5.25)	3.02 (1.31–7.01)	0.006
Model 2[a]	1	2.64 (1.28–5.45)	3.32 (1.41–7.79)	0.003
Model 3[a]	1	2.53 (1.23–5.23)	2.29 (0.87–6.01)	0.04
Ischemic strokes				
Cases, *n*	8	20	9	
Incidence rates/1000 person-years	1.7	4.6	6.2	
Model 1[a]	1	2.16 (0.95–4.92)	2.84 (1.09–7.37)	0.02
Model 2[a]	1	2.15 (0.94–4.93)	2.86 (1.09–7.49)	0.03
Model 3[a]	1	2.10 (0.92–4.82)	2.28 (0.78–6.67)	0.09

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, model 3: adjusted for model 2 plus diabetes.

4. Discussion

This is the first report of a prospective cohort study showing that serum 1,5-AG levels predict CVD incidence in men, similar to HbA_{1c} [15–17] or postload glucose levels in OGTT [4,5]. More subjects with overt diabetes were included in the category with serum 1,5-AG levels of 14.0 μg/mL or less, which would lead to the greatest risk. Those with serum 1,5-AG levels of 14.1 to 24.4 μg/mL, whose preva-

Table 3
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥21.3	14.1–21.2	≤14.0	
Person-years	5077	5293	2424	
All cardiovascular diseases				
Cases, *n*	22	15	13	
Incidence rates/1000 person-years	4.3	2.8	5.4	
Model 1[a]	1	0.83 (0.43–1.60)	1.23 (0.62–2.44)	0.68
Model 2[a]	1	0.92 (0.47–1.79)	1.30 (0.65–2.60)	0.54
Model 3[a]	1	0.91 (0.47–1.77)	1.04 (0.48–2.22)	0.99
Coronary heart disease				
Cases, *n*	7	5	7	
Incidence rates/1000 person-years	1.4	0.9	2.9	
Model 1[a]	1	0.82 (0.26–2.60)	2.09 (0.73–5.96)	0.21
Model 2[a]	1	0.89 (0.28–2.83)	2.33 (0.81–6.71)	0.15
Model 3[a]	1	0.87 (0.27–2.76)	1.74 (0.54–5.56)	0.42
All strokes				
Cases, *n*	15	10	6	
Incidence rates/1000 person-years	3.0	1.9	2.5	
Model 1[a]	1	0.83 (0.37–1.86)	0.83 (0.32–2.14)	0.65
Model 2[a]	1	0.93 (0.41–2.09)	0.88 (0.34–2.27)	0.77
Model 3[a]	1	0.92 (0.41–2.08)	0.75 (0.26–2.12)	0.59
Ischemic strokes				
Cases, *n*	6	7	3	
Incidence rates/1000 person-years	1.2	1.3	1.2	
Model 1[a]	1	1.48 (0.50–4.41)	1.03 (0.26–4.12)	0.84
Model 2[a]	1	2.01 (0.66–6.11)	1.20 (0.29–4.89)	0.60
Model 3[a]	1	1.99 (0.66–6.06)	1.01 (0.22–4.71)	0.71

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL-cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, menopause, model 3: adjusted for model 2 plus diabetes.

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Table 4
Incidence rates and adjusted hazard ratios for coronary heart disease and ischemic strokes by serum 1,5-anhydro-D-glucitol levels in men and women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥23.1	14.1–23.0	≤14.0	
Number of subjects	854	865	376	
Person-years	9606	9814	3878	
Coronary heart diseases				
Cases, *n*	22	25	17	
Incidence rates/1000 person-years	2.3	2.5	4.4	
Model 1[a]	1	1.36 (0.76–2.44)	2.17 (1.14–4.13)	0.02
Model 2[a]	1	1.41 (0.78–2.52)	2.10 (1.10–4.02)	0.03
Model 3[a]	1	1.37 (0.76–2.46)	1.76 (0.85–3.63)	0.12
Ischemic strokes				
Cases, *n*	19	22	12	
Incidence rates/1000 person-years	2.0	2.2	3.1	
Model 1[a]	1	1.25 (0.67–2.31)	1.58 (0.76–3.27)	0.22
Model 2[a]	1	1.24 (0.67–2.31)	1.56 (0.75–3.24)	0.23
Model 3[a]	1	1.21 (0.65–2.25)	1.23 (0.54–2.82)	0.56

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, sex, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

lence of diabetes or anti-diabetic medication was clearly lower than those with 14.0 μg/mL or less, also had significantly elevated risks. This suggested the possibility that many subjects without overt diabetes who had postprandial hyperglycemia with excretion of glucose in the urine were included in this middle category. Measurement of serum 1,5-AG levels can be useful to detect individuals at greater risk for CVD even among those without overt diabetes. In fact, the sensitivity analyses in non-diabetic subjects with almost normal plasma glucose levels also showed similar results, which reinforced these findings.

In men, the relationship between serum 1,5-AG levels and stroke was much clearer than that with CHD. The prevalence of hypertension increased with decrease in serum 1,5-AG levels, but the prevalence of hypercholesterolemia did not change, irrespective of serum 1,5-AG levels. Such discrepancies in the relationships between serum 1,5-AG levels and risk factors for CVD may account for the difference observed between risk of stroke and that of CHD.

In women, no significant relationship was observed between serum 1,5-AG levels and the risk for all CVD or each CVD subtype, although a similar increase in the risk for CHD was found. Previous meta-analyses have shown either that women with diabetes have a higher risk for CHD than men with diabetes [18,19], or that there was no sex difference [20]. The DECODE study also showed that the HR of death from CVD in individuals with 2-h glucose levels of 11.1 mmol/L or greater tended to be higher among women than among men [5]. The present results show an opposite sex difference, and the reason is not clear. However, the prevalence of diabetes at baseline was much lower in women than in men, and the incidence rate of all CVD and each CVD subtype was also relatively lower in women. Such discrepancies in basic characteristics

Table 5
Sensitivity analyses of incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in non-diabetic men with fasting or postprandial plasma glucose levels of less than 6.1 mmol/L, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	388	349	77	
Person-years	4326	3636	703	
All cardiovascular diseases				
Cases, *n*	22	40	8	
Incidence rates/1000 person-years	5.1	11.0	11.4	
Model 1[a]	1	1.75 (1.04–2.96)	1.65 (0.73–3.72)	0.07
Model 2[a]	1	1.76 (1.04–2.98)	2.00 (0.88–4.55)	0.03
Coronary heart diseases				
Cases, *n*	14	17	2	
Incidence rates/1000 person-years	3.2	4.7	2.8	
Model 1[a]	1	1.26 (0.62–2.57)	0.71 (0.16–3.15)	0.96
Model 2[a]	1	1.18 (0.57–2.43)	0. 86 (0.19–3.86)	0.89
All strokes				
Cases, *n*	8	23	6	
Incidence rates/1000 person-years	1.8	6.3	8.5	
Model 1[a]	1	2.58 (1.15–5.79)	3.11 (1.07–9.00)	0.01
Model 2[a]	1	2.51 (1.11–5.66)	3.68 (1.26–10.75)	0.01
Ischemic strokes				
Cases, *n*	7	15	5	
Incidence rates/1000 person-years	1.6	4.1	7.1	
Model 1[a]	1	1.97 (0.80–4.85)	3.05 (0.96–9.69)	0.045
Model 2[a]	1	1.92 (0.77–4.75)	3.45 (1.08–11.05)	0.03

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

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between men and women might result in the sex difference. In addition, the involvement of selection bias cannot be completely eliminated in women. Further studies with sufficient samples and CVD events in women are necessary to clarify this problem.

Measurement of serum 1,5-AG levels could detect not only those with persistent hyperglycemia but also those with transient postprandial hyperglycemia who are likely to be at higher risk for development of diabetes in the near future. Accordingly, decrease in serum 1,5-AG levels might be related with the elevated risk of CVD. The previous epidemiological studies also reported the association of postprandial hyperglycemia with risk of CVD [4–6], and the present results are not inconsistent with them. However, the mechanism remains still inconclusive, and two hypotheses could be considered. First, hyperglycemia itself is a risk for atherosclerotic diseases. Second, hyperglycemia is just a reflection of insulin resistance which is closely related to risk factors for atherosclerotic diseases. In the present study, adjustments for insulin resistance-related factors, waist circumferences or triglycerides, hardly changed the results. This indirectly suggests that serum 1,5-AG levels are independently related with a risk for CVD from insulin resistance, and we infer that hyperglycemia itself might be a risk.

OGTT cannot be conducted easily in the routine clinical setting or during health check-ups because it requires overnight fasting in blood sampling, longer time and extra costs. Conversely, measurement of serum 1,5-AG can be performed easily with a single non-fasting blood sample and is relatively low cost. Serum 1,5-AG levels do not fluctuate very much within an individual if glucose is not excreted into urine; however, it varies widely among individuals [1–3,13,21,22]. Accordingly, periodic measurement of serum 1,5-AG might be important for the early detection of a decrease from the normal level in each individual.

It is also well known that hemoglobin A_{1c} (HbA_{1c}) is useful for the diagnosis of diabetes or as a marker of glycemic control, and elevated HbA_{1c} is associated with increased risk for macro- and micro-complications [15–17,23]. HbA_{1c} can also be measured in a single non-fasting blood sample. However, red cell turnover and hemoglobinopathies influence HbA_{1c} levels, and this has been often identified as a problem [23,24]. In contrast, serum 1,5-AG levels are not affected by red cell turnover and hemoglobinopathies. In terms of screening higher risk individuals among the general population, a combination of HbA_{1c} and serum 1,5-AG measurements might be better choice.

The present analysis had several limitations. First, some aspects of medical history were unknown, including gastric resection, hyperthyroidism and renal glycosuria, which can lower 1,5-AG levels. Second, the present dataset did not include measurement of HbA_{1c} levels or OGTT; therefore, comparison of HbA_{1c} or OGTT with serum 1,5-AG was not possible. Third, a single serum 1,5-AG measurement at baseline may have lead to an underestimation of the association between serum 1,5-AG levels and CVD due to regression dilution bias [25].

In conclusion, the present analyses suggest that in men measurement of serum 1,5-AG was useful to detect individuals at increased risk for CVD, regardless of the presence or absence of diabetes. Measurement of serum 1,5-AG levels might be a useful tool for screening in the clinical setting or during health check-ups. However, this is the first report with a limited population of Japanese, and these findings should be further investigated by studies with sufficient samples and CVD events among various populations, races and geographical areas.

Conflict of interest

None to be declared.

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Importance of cerebral artery risk evaluation before off-pump coronary artery bypass grafting to avoid perioperative stroke

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Abstract

Objective: Cerebrovascular atherosclerotic disease is a widely known risk factor for stroke after conventional coronary artery bypass grafting (CABG). The aim of this study is to evaluate the incidence of stroke in patients with significant cerebrovascular disease after off-pump CABG. **Methods:** In this retrospective study, 611 patients, who underwent off-pump CABG, were divided into high-risk ($n = 196$) and low-risk groups ($n = 415$) for perioperative stroke using preoperative brain magnetic resonance angiography/imaging and cervical Doppler sonography, and the incidence of stroke in the two groups was compared. **Results:** No 'intra-operative' stroke was observed. However, seven patients (3.6%) in the high-risk group and one patient (0.2%) in the low-risk group developed 'delayed stroke' between the day of surgery and postoperative day 18 (mean postoperative day 8.8). The predominant aetiology of delayed stroke was thrombo-embolism. Assignment to the high-risk group had a significant association with the occurrence of delayed stroke ($p = 0.011$). The person-time incidence rate of stroke in the high-risk group was much higher within 1 month (3.57) after CABG than beyond 1 month (0.14). **Conclusions:** Patients with significant cerebrovascular disease did not develop intra-operative stroke after off-pump CABG. However, these patients were likely to suffer from delayed stroke within 30 days of surgery.

Keywords: Coronary artery bypass grafting; Off-pump; Cerebrovascular disease; Stroke

1. Introduction

The aetiology of stroke after coronary artery bypass grafting (CABG) is complex and multifactorial, and it may include systemic inflammatory response, cerebral embolism and cerebral hypoperfusion. Intra-operative release of atherosclerotic emboli associated with aortic cannulation and cross-clamping is believed to be the most important risk factor [1]. Because off-pump CABG can decrease aortic manipulation, this technique has been expected to reduce the incidence of stroke. However, some meta-analyses have failed to demonstrate a significant benefit of off-pump CABG in reducing the rate of perioperative stroke [2,3].

Most previous studies defined stroke as an event occurring over the course of the entire hospital stay and have not focussed on the timing of stroke. More than half of the strokes occurred after the patients fully recovered from the effect of anaesthesia without any neurological deficit [4,5]. The causes of these 'delayed strokes' also seem to be multifactorial, and few studies have specifically addressed the incidence and aetiology of delayed stroke after off-pump CABG.

In addition to cerebral emboli derived from aortic atherosclerosis, patients undergoing CABG are likely to have severe atherosclerosis of the carotid/cranial arteries. The presence of cerebrovascular disease is also a widely accepted risk factor for stroke [6]. The aim of this study was to examine the impact of cerebrovascular disease on the incidence and timing of stroke after off-pump CABG.

2. Materials and methods

2.1. Study group

Between January 1997 and December 2008, 707 patients underwent off-pump CABG in our institution. Among them, 611 patients, who underwent a preoperative screening examination involving brain magnetic resonance imaging (MRI), brain magnetic resonance angiography (MRA) and cervical Doppler ultrasonography, were enrolled in this retrospective study. The 611 patients were divided by neurologists into two groups (high-risk and low-risk) on the basis of the presence or absence of carotid or intracranial artery stenosis and past history of stroke according to an algorithm shown in Fig. 1.

2.2. Surgical techniques

In almost all cases, off-pump CABG was performed through a median sternotomy. Proximal anastomoses of free conduits

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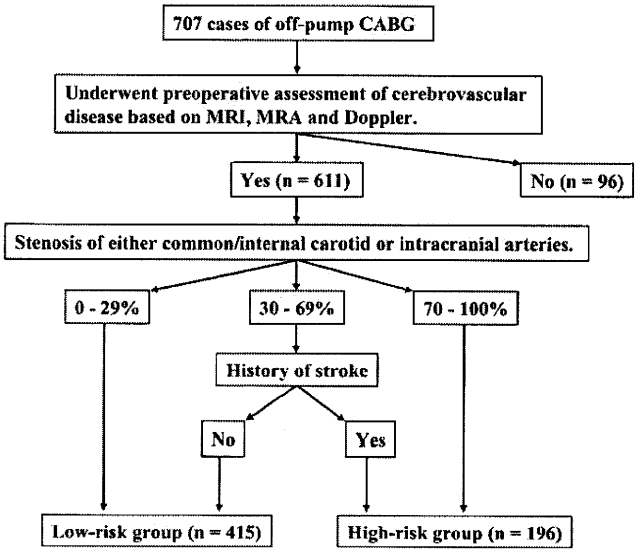

Fig. 1. Algorithm for risk assessment of perioperative stroke after coronary artery bypass grafting. CABG: coronary artery bypass grafting; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

(saphenous vein and radial artery) were placed on the ascending aorta using less invasive anastomotic devices such as Aortic connector (St. Jude Medical Inc., St Paul, MN, USA), Heartstring (Guidant, Indianapolis, IN, USA), and Enclose (Novare Surgical Systems, Cupertino, CA, USA) rather than using a partial aortic clamp. When intra-operative epi-aortic ultrasonography revealed significant atherosclerotic disease, an aortic no-touch technique was applied using the free conduits as Y or I extensions on the *in situ* internal thoracic artery graft (composite graft).

2.3. Perioperative anti-platelet/anticoagulation protocol

The intake of all anti-platelet agents, including aspirin, was suspended 7 days before surgery, except in patients with unstable angina and tight left main disease. Subcutaneous heparin was administered until the day before surgery. During CABG, intravenous heparin was administered to achieve an activated clotting time of greater than 300 s, and it was neutralised at the end of the procedure with protamine sulphate. The administration of aspirin was reinitiated on the day after surgery. Warfarin treatment was also initiated in patients, who had received a vein graft.

2.4. Definitions

Stroke was defined as a new neurological deficit lasting for more than 24 h. If the neurological deficit was present when the patient emerged from anaesthesia, the stroke was defined as 'intra-operative stroke'. 'Delayed stroke' was defined as a stroke occurring after the patient fully recovered from the effect of anaesthesia without neurological deficit and if it occurred within 1 month of surgery. Stroke was diagnosed by neurologists and confirmed by brain MRI or computed tomography (CT). Renal failure was defined as a serum creatinine level of greater than 1.5 mg dl^{-1} or the requirement for haemodialysis. Low cardiac output syndrome (LOS) was defined as the use of postoperative inotropic support for more than 48 h. Perioperative myocardial infarction (PMI) was diagnosed if the level of serum creatine kinase MB isoenzyme was more than 100 IU l^{-1}.

The occurrence of stroke (stroke rate) was expressed as a person-time incidence rate [7]. Incidence per 100 person-months, r, is defined by the following equation: $r = (N/D) \times 100$, where N is the number of strokes occurring during the observation period and D is person-time units (months).

2.5. Statistical analysis

Numerical variables are presented as the mean ± stan-standard deviation for each patient group and compared using the Mann–Whitney test. Categorical variables are given as percentages and compared using the chi-square and Fisher's exact tests where appropriate. Event-free ratio analysis was performed with the Kaplan–Meier method, and statistical significance was calculated with the log-rank test. Univariate analysis, expressed as odds ratio with 95% confidence interval limits and p values, was used to evaluate the effect of preoperative and postoperative variables on the occurrence of neurologic complications. Statistical significance was accepted at $p < 0.05$. Analyses were performed using the SPSS statistical software (version17.0; SPSS Inc., Chicago, IL, USA).

3. Results

Of the 611 patients who underwent the risk assessment for perioperative stroke before surgery, 196 patients (32%) were considered to be at high risk for stroke. None of these patients had experienced a recent episode of cerebrovascular accident (CVA), nor did any of them require previous or concomitant carotid artery intervention. The remaining 415 patients (68%) were considered to be at low risk for perioperative stroke. The preoperative characteristics of the groups are summarised in Table 1. Patients in the high-risk group were older, had a higher prevalence of diabetes and renal failure and a greater average number of diseased coronary vessels. In 423 cases out of the entire 611, off-pump CABG cases, the anastomotic devices were available. Of those, 241 cases used free conduits, and 15.8% of them required aortic no-touch technique after assessment using epi-aortic ultrasonography.

Table 2 lists the observed postoperative results. No intra-operative stroke occurred in either group. However, seven patients (3.6%) in the high-risk group developed delayed stroke after an initially uncomplicated neurologic course, in

Table 1
Preoperative characteristics.

	High-risk (n = 196)	Low-risk (n = 415)	p value
Male	77.0%	79.8%	0.44
Age (years)	69.7 ± 7.6	66.6 ± 9.4	<0.001
Diabetes	54.1%	42.8%	0.009
Renal failure	19.7%	12.0%	0.012
LVEF (%)	59.8 ± 15.6	62.4 ± 14.0	0.10
No. of diseased vessel	2.6 ± 0.6	2.4 ± 0.7	0.001

LVEF: left ventricular ejection fraction.